



Fax

To: Dr. George Karkanas

From: Krysta Gorman

Cytira

LifeSpan BioSciences, Inc.

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Re: Cyt 001a

CC:

Pages: 7 including cover

Date: 10/30/06

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

● **Comments:**

Please find the fully executed Research Agreement identified as Cyt 001a for your records to follow.

Best regards,

A handwritten signature in black ink, appearing to read "Krysta Gorman". The signature is fluid and cursive.

Krysta Gorman

Contracts Administration Coordinator

Cytira Inc. / LifeSpan BioSciences Inc. Research Agreement

Contact Name: George Karkanias
Study Type: Contract IHC
Contract ID: CYTI001a
Proposal No.: P00206.v3.CYTI

This **RESEARCH AGREEMENT**, effective as of the last date signed, is made and entered into by and between LifeSpan BioSciences Inc. ("LifeSpan"), a Washington corporation at 2401 4th Avenue Suite 900, Seattle WA 98121, and Cytira Inc. ("Cytira"), at 305 Madison Avenue, Suite 449, New York, NY 10165.

PROPOSED STUDY:

The purpose of this study is to use Immunohistochemistry (IHC) to determine the distribution and localization of Estrogen Receptor Alpha (ER Alpha), Estrogen Receptor Beta (ER Beta), Estrogen Related Receptor Alpha (ERR Alpha) & Estrogen Related Receptor Gamma (ERR Gamma) in normal and experimental mouse brain tissue specimens, using antibodies supplied by LifeSpan and normal and experimental mouse brain tissue specimens provided by Cytira.

CUSTOMER STATEMENT OF STUDY GOALS:

The goal of this study is to evaluate the expression frequency of four proteins (ER Alpha, ER Beta, ERR Alpha & ERR Gamma) in 20 regions and subregions of the hypothalamus from normal and experimental mouse tissue specimens.

CUSTOMER SUPPLIED DATA AND INFORMATION:

All customer information pertaining to this study must be disclosed below. Disclosure of information after the execution of this agreement may change the scope of the study and additional fees may apply.

Cytira will supply LifeSpan with normal (N=3) and experimental (N=3) mouse brain tissue specimens prepared using LifeSpan's protocol for formalin fixation of tissues. On receipt of the brain tissues, LifeSpan will perform tissue preparation, validation and mapping steps in order to isolate the 20 regions and subregions of the hypothalamus to be examined in this study.

LifeSpan will provide all other reagents for the execution of this study including primary antibodies.

Cytira will supply LifeSpan with a list of IP addresses that will be allowed access to the web interface to view the online reports. LifeSpan will use the combination of IP addresses with usernames and passwords to ensure the security of confidential information published through the LifeSpan online interface.

Control Tissue Information

Final selection of control tissues will be made by LifeSpan and will take into consideration those tissues recommended by the client below.

1. Target Name:	Estrogen Receptor Alpha (ER Alpha)
Human Target Accession:	
Positive Controls	Negative Controls
1: Mouse Tissue	1: Mouse Tissue
2: Mouse Tissue	2: Mouse Tissue

2. Target Name:	Estrogen Receptor Beta (ER Beta)
Human Target Accession:	
Positive Controls	Negative Controls
1: Mouse Tissue	1: Mouse Tissue
2: Mouse Tissue	2: Mouse Tissue

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3. Target Name:	Estrogen Related Receptor Alpha (ERR Alpha)
Human Target Accession:	
Positive Controls	Negative Controls
1: Mouse Tissue	1: Mouse Tissue
2: Mouse Tissue	2: Mouse Tissue

4. Target Name:	Estrogen Related Receptor Gamma (ERR Gamma)
Human Target Accession:	
Positive Controls	Negative Controls
1: Mouse Tissue	1: Mouse Tissue
2: Mouse Tissue	2: Mouse Tissue

Antibody Information

Antibody #1	To be supplied by LifeSpan
Antibody Name:	Anti- ER Alpha antibody
Target Name:	Estrogen Receptor Alpha (ER Alpha)
Human Target Accession:	
Antibody Source:	Affinity Bioreagents
Antibody Catalog Number:	PA1-309
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #2	To be supplied by LifeSpan
Antibody Name:	Anti- ER Alpha antibody
Target Name:	Estrogen Receptor Alpha (ER Alpha)
Human Target Accession:	
Antibody Source:	Santa Cruz
Antibody Catalog Number:	SC-543
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #3	To be supplied by LifeSpan
Antibody Name:	Anti- ER Beta antibody
Target Name:	Estrogen Receptor Beta (ER Beta)
Human Target Accession:	
Antibody Source:	Affinity Bioreagents
Antibody Catalog Number:	PA1-310B
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #4	To be supplied by LifeSpan
Antibody Name:	Anti- ER Beta antibody
Target Name:	Estrogen Receptor Beta (ER Beta)
Human Target Accession:	
Antibody Source:	Santa Cruz
Antibody Catalog Number:	SC-8974
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #5	To be supplied by LifeSpan
Antibody Name:	Anti- ERR Alpha antibody
Target Name:	Estrogen Related Receptor Alpha (ERR Alpha)
Human Target Accession:	
Antibody Source:	MBL International
Antibody Catalog Number:	LS-A5480
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #6	To be supplied by LifeSpan
Antibody Name:	Anti- ERR Alpha antibody
Target Name:	Estrogen Related Receptor Alpha (ERR Alpha)
Human Target Accession:	
Antibody Source:	Upstate
Antibody Catalog Number:	07-662
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #7	To be supplied by LifeSpan
Antibody Name:	Anti- ERR Gamma antibody
Target Name:	Estrogen Related Receptor Gamma (ERR Gamma)
Human Target Accession:	
Antibody Source:	Aviva
Antibody Catalog Number:	ARP31655 T200
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

Antibody #8	To be supplied by LifeSpan
Antibody Name:	Anti- ERR Gamma antibody
Target Name:	Estrogen Related Receptor Gamma (ERR Gamma)
Human Target Accession:	
Antibody Source:	MBL International
Antibody Catalog Number:	LS-A5960
Antibody Clonality:	Rabbit, polyclonal
Additional Note:	

GENERAL STUDY DESCRIPTION:

This study will consist of two phases:

Phase I: LifeSpan will characterize the activity of the eight (8) antibodies in IHC. Using LifeSpan's standardized IHC protocol, a 5-step serial dilution of each antibody will be run using the positive and negative formalin-fixed paraffin-embedded (FFPE) control tissues listed above and the results interpreted by a LifeSpan Pathologist.

At the conclusion of Phase I, a Phase I report will be delivered to the customer containing a summary of the results, digital images, and LifeSpan's recommendation as to which one (1) antibody / target protein should be selected for use in Phase II, and/or recommend assay optimization procedures if necessary. In the event that assay optimization efforts are necessary in order to maximize an antibodies performance, additional fees would apply and require an addendum to this agreement. The customer can elect to either continue or cancel the study without any further obligation to LifeSpan.

For antibody stability reasons, LifeSpan requires that the customer response to proceed to Phase II occur within one (1) month after delivery of the Phase I results. Any study where this response to proceed falls outside of this timeframe will incur an antibody re-titering fee of \$175 per antibody.

Phase II: Using one (1) antibody / target protein, LifeSpan will determine the distribution and localization of the four (4) target proteins (ER Alpha, ER Beta, ERR Alpha & ERR Gamma) in the following twenty (20) regions and subregions of the hypothalamus from the following six (6) formalin-fixed paraffin embedded mouse normal and experimental brain tissues supplied by Cytira.

20 Hypothalamus regions and sub-regions:

anteroventral periventricular nucleus (AVPe)
 lateral hypothalamic area (LH)
 lateral preoptic area (LPO)
 median eminence (ME)
 periaqueductal gray (PAG)
 preoptic area (PO)
 ventrolateral preoptic nucleus (VLPO)
 ventromedial preoptic nucleus (VMPO)
 anterodorsal preoptic nucleus (ADP)
 medial preoptic nucleus (MPO)
 medial preoptic nucleus, central part (MPOC)
 medial preoptic nucleus, lateral part (MPOL)
 medial preoptic nucleus, medial part (MPOM)
 ventrolateral hypothalamic nucleus (VLH)
 dorsomedial hypothalamic nucleus (DMN)
 ventromedial hypothalamic nucleus (VMH)
 ventromedial hypothalamic nucleus, anterior part (VMHA)
 ventromedial hypothalamic nucleus, central part (VMHC)
 ventromedial hypothalamic nucleus, dorsomedial part (VMHDM)
 ventromedial hypothalamic nucleus, ventrolateral part (VMHVL)

FROM:

Normal Mouse (N=3)

Experimental Mouse (N=3)

REPORTING OF RESULTS:

At the conclusion of this study, LifeSpan will provide Cytira with a **FULL TEXT** report of the Phase II results including **DIGITAL IMAGES**. In the report LifeSpan will provide a comprehensive analysis of the tissue sections and also perform a statistical analysis to show whether each region and sub-region from the treatment groups are different from each other, i.e. increase or decrease in expression of target proteins among the groups rather than just presence or absence of positive cells. LifeSpan will also calculate the number of positive cells in each region and sub-region resulting in an average across the animals in each group and hence there will be a mean +/- some variance across the control and experimental groups for each region and sub-region. The report will be provided via a secure website, viewable for one year from publication. Upon request, reports and images can also be supplied on CD-ROM for an additional fee of \$75.

PRICING TERMS:

All additional pathology work will be billed at \$200 per hour. All other additional work will be billed at \$150 per hour. Additional work will require an addendum to this contract. In the event that additional antibody Units are required to complete the study, Cytira will be notified and the associated cost added to the final invoice. In the event that the client would like to loan the study slides, a fee of \$500 will apply for preparation and shipping. The slides will be loaned for a period of 60 days, after which a \$500/month penalty fee will apply.

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TOTAL COST:

Antibody Materials: The price for purchasing the eight commercial antibodies will be added to the final invoice.

Phase I: \$6,440 (\$1,025 for 1st Antibody and \$585 for subsequent antibodies to same target)

**Phase II: Materials
Tissue Preparation +
Validation** \$1,890 (\$315 per tissue x 6 tissues)

**Phase II: Materials
Tissue Mapping:** \$1,800 (\$300 per tissue x 6 tissues)

**Phase II: IHC,
Analysis and
Reporting** Full Text Report with Images
\$450 Study Setup Fee
\$21,744 (\$906 x 4 abs x 6 tissues)

Total	Stage	Price
	Phase I: FFPE	\$6,440 + cost of commercial antibodies
	Phase II: Materials	\$3,690
	Phase II: IHC	\$22,194
	Total:	\$32,324 + cost of commercial antibodies

STUDY PERIOD:

The Study Period will be initiated upon LifeSpan receipt of a fully executed agreement AND all biological materials, including, but not limited to, all antibodies and tissues required to conduct the study. LifeSpan estimates that the Study will be completed within eight (8) weeks of study initiation. In the case that assay optimization procedures are necessary the study period will increase proportionally to these efforts.

CONTACT INFORMATION:

LifeSpan Sales Representative	Cytira Scientific Contact
Harjit S. Kullar	George Karkanas
Harjit.Kullar@lsbio.com	george.karkanas@cytira.com
(508) 376-8277	(212) 372-9654

Cytira hereby retains LifeSpan on a confidential basis to perform studies and/or tests and prepare one or more reports in accordance with the terms and conditions attached to this order form.

LifeSpan BioSciences, Inc.

Cytira, Inc.

Name: *Glenna C. Burner*
 Title: Chief Scientific Officer
 Company: LifeSpan BioSciences, Inc.

Date

Name: *George Karkanas*
 Title: *Managing Partner*
 Company: *Cytira*

Date

Terms and Conditions

1. Payment Terms

Customer will pay LifeSpan the sums set forth in its Study Proposal within thirty (30) days after the invoice date. Any payments overdue from Customer to LifeSpan shall accrue interest at a rate of 1.5% per month, compounded quarterly. The Scope of Work under this Agreement may be modified only by a written addendum signed by both parties. Unless otherwise specified in an addendum, the Phase I price will be invoiced upon signing by both parties, 50% of the Phase II price will be invoiced upon initiation of Phase II, and the remaining 50% of the Phase II price will be invoiced upon delivery of final results. Please direct billing inquiries to LifeSpan at (206) 464-1554.

The payments made by Customer under this Agreement do not include any applicable retail sales, use, or similar taxes. Customer shall be responsible for reporting and paying any applicable retail sales, use, or similar taxes imposed on Customer or LifeSpan with respect to the services provided by LifeSpan to Customer under this Agreement. Customer shall reimburse and hold LifeSpan harmless for any retail sales, use, or similar taxes, plus any interest and penalties, imposed or assessed against LifeSpan by any taxing jurisdiction with respect to the services provided by LifeSpan to Customer under this Agreement.

2. Customer Materials

It is contemplated that tangible materials, information, electronic data and/or written documents will be provided by or on behalf of Customer for LifeSpan's use in performing this Agreement (hereinafter collectively "Customer Materials"). To the extent that such Customer Materials are owned by or licensed to Customer, they shall be treated as the exclusive property of Customer. All reports created by LifeSpan pursuant to this Agreement and all knowledge or information about Customer Materials that is discovered or derived by LifeSpan within the scope of performing its work under this Agreement shall also be the exclusive property of Customer. Customer shall have the exclusive right to publish any such knowledge or information for any lawful purpose or to incorporate it into Customer's product(s), provided that Customer may not commercially resell LifeSpan's raw data to unaffiliated third parties who might otherwise be customers of LifeSpan. This Agreement shall not be construed as transferring or licensing any patent right, copyright, or other proprietary right of Customer to LifeSpan except as reasonably required for LifeSpan to perform its Scope of Work. At the same time, LifeSpan's completion of proprietary studies for Customer shall not preclude LifeSpan from performing subsequent independent studies of the same gene(s) or antibodies for others or for its own research. If Customer hereafter decides to file a patent application covering property assigned to Customer under this Agreement, LifeSpan shall, at Customer's request and expense, reasonably assist Customer in preparing and prosecuting such application.

3. LifeSpan Technology

In performing under this Agreement, it is contemplated that LifeSpan will utilize its existing proprietary software, technology, inventions and know-how related to recovery of genetic information from human tissue samples and use of peptide information to make antibodies and reagents (hereinafter collectively "LifeSpan Technology"). Such LifeSpan Technology shall be treated as the exclusive property of LifeSpan. All new knowledge or information discovered or derived by LifeSpan pertaining to analytic methods or peptide design used in antibody generation in the course of performing this Agreement, except for items specifically assigned to Customer herein, shall also be the exclusive property of LifeSpan (including without limitation any process improvements in *in situ* hybridization, immunohistochemistry, high-density arrays, or knowledge of specific peptide sequences that are used to generate antibodies or reagents for immunohistochemistry or for diagnostic purposes), provided that LifeSpan shall grant Customer a non-assignable non-exclusive license to use peptide sequences internally. For those studies in which the deliverables include a detailed protocol of the optimized assay conditions, said protocol will be the exclusive property of LifeSpan, to which LifeSpan will grant the Customer a perpetual, non-assignable non-exclusive license for use in those specific applications defined within the terms of the Agreement. Except as specifically provided in Section 2 hereof, this Agreement shall not be construed as transferring or licensing any patent right, copyright, or other proprietary right of LifeSpan to Customer.

4. LifeSpan Materials

It is contemplated that LifeSpan shall furnish human tissue samples and/or slides thereof and antibodies and/or reagents for use in performing its work (hereinafter collectively "LifeSpan Materials"). All LifeSpan Materials shall remain the exclusive property of LifeSpan. For those studies in which LifeSpan produces antibody, Customer will receive all remaining affinity purified antibody and frozen serum once the study is complete and so long as LifeSpan supplies exceed an archive sample of one milliliter that may be retained by LifeSpan. Antisera delivered by LifeSpan to Customer under this Section 4 shall become the property of the Customer. For a period of five (5) years after the Effective Date of this Agreement, however, the slides relating to LifeSpan's Scope of Work shall be available for up to sixty (60) days of loan for confidential examination by Customer's scientists, collaborators and consultants. Such slides shall be used solely in connection with the Scope of Work under this Agreement and shall not be disclosed to any third party that has not first agreed in writing to the confidentiality restrictions hereunder.

5. Confidentiality

The parties acknowledge that Customer's Materials, LifeSpan Technology, and LifeSpan Materials include proprietary information (whether patented or unpatented), and each party shall take diligent steps to assure that such proprietary information is maintained in strict confidence at all times. Neither party shall disclose materials or technology belonging to the other party except to third persons who have bound themselves in writing to honor the confidentiality restrictions of this section. Also, LifeSpan shall not disclose the subject or substance of its Scope of Work under this Agreement to any third party without Customer's prior written consent. To the extent that Customer acquires knowledge of LifeSpan's proprietary methods under this Agreement, such knowledge shall be used solely for Customer's internal evaluation of LifeSpan's work. Confidential information shared or otherwise obtained in connection with this Agreement shall not be disclosed without the disclosing party's written consent for at least five (5) years after the date of its initial disclosure hereunder. This confidentiality restriction does not apply to information that is already in the public domain or to information that was developed independently of the disclosing party.

6. Changes

In the event that Customer requests additions to the agreed Scope of Work hereunder, a change order form ("Change Order") will be prepared by LifeSpan and signed by both parties before commencement of the additional work. The change order form will stipulate the hourly charges or fixed price for the additional work. The obligations in Sections 2-5 above shall survive a termination of this Agreement.

7. Statement of Ethics

LifeSpan BioSciences combines expertise in medicine and engineering with other disciplines. Company policy requires each officer and employee to comply strictly with the ethical rules of his or her profession. Tissue samples are obtained from reputable medical institutions whose conduct is subject to governance by institutional review boards (IRBs). To the best of LifeSpan's knowledge, each such institution has collected its samples and obtained informed consents to the extent required by applicable laws, regulations and ethical standards.

8. Term and Termination

The term of this Agreement shall be six (6) months from the last date of signature ("Effective Date"), but can be extended by mutual written agreement. Either party may terminate this Agreement in the event of any material breach of the Agreement that is not cured within thirty (30) days following written notice thereof. LifeSpan may also terminate this Agreement upon thirty (30) days' written notice for convenience. Customer may terminate this Agreement for convenience upon thirty (30) days' notice to LifeSpan (the "Termination Date"). In such event, LifeSpan shall cease work immediately after receiving notice from Customer, unless the parties agree otherwise. Upon early termination of work, Customer shall pay LifeSpan the percentage of total payment which is equal to the percentage of study costs that LifeSpan has incurred or for which it has become obligated up to and including the Termination Date. To the extent that Customer has prepaid any amounts in excess of the amount due, LifeSpan shall credit to Customer that portion of the prepaid fees.